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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/234,028	01/20/1999	RONALD T. RAINES	960296.95360	6579

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EXAMINER	
HUTSON, RICHARD G	
ART UNIT	PAPER NUMBER
1652	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/234,028	RAINES, RONALD T.	
	Examiner	Art Unit	
	Richard G. Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9,10,15 and 16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9,10,15 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/24/2006 has been entered.

Applicants amendment of claims 1, 9 and 15, and the addition of new claim 16, in the paper of 7/24/2006 and 10/18/2006, is acknowledged. Claims 1-7, 9, 10, 15 and 16 are at issue and are present for examination.

Applicants' arguments filed on 7/24/2006 and 10/18/2006, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Newly amended claim 1's recitation "...only by having at least one amino acid substitution ..." is indefinite in that it is unclear and confusing what this phrase means. While it appears that applicants are trying to place a limitation on the subject invention by the use of "only", this is unclear given the combination of "only" with "at least". For the purposes of advancing prosecution the phrase is interpreted as "...having at least one amino acid substitution ...".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, 9, 10 and 15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This rejection was stated in the previous office action as it applied to claims previous claims 1-7, 9, 10 and 15. In response to the previous rejection, applicants have canceled claim 8 and amended claims 1, 9 and 15 and traverse the rejection in combination with the rejection based on a lack of enablement below, as it applies to the newly amended claims.

Applicants continue to traverse this rejection on the basis that the claims of the present application recite clear unambiguous structural characteristics that both distinguish the prior art and that are also tightly linked to the chemical phenomenon that

the applicants have utilized to make improvements to ribonuclease inhibitor variants. Applicants submit that every claim in the application is limited by a specific amino acid change from native ribonuclease inhibitor, the substitution of a cysteine by a residue that will not form a disulfide bond.

Applicants submit that the claimed variants are defined by amino acid changes to the amino acid sequences of claimed protein variants. Applicants further submit that there is also functional language that supports the structural claim language and does not diminish it.

Applicants further question how claim 15 was included in the current rejection as it claims a human ribonuclease variant, which applicants submit they have exemplified in their specification.

Applicant's complete argument is acknowledged and has been carefully considered, however, continues to be found non-persuasive. Applicant's arguments continue to be along the same principal of reason previously argued. Applicants amendments to the claims continue to be directed to the "means by which" the final product is obtained, rather then to the actual final claimed product (i.e. the ribonuclease inhibitor variant or mutant). As these means or processes do not place limitations on the final claimed product, applicants have not thus limited the scope of the claimed product and the scope of the claimed product continues to not be adequately described for the reasons previously stated.

Applicants continue to be reminded that while applicants specification provides two examples of ribonuclease inhibitors variants that could be the result of those

"process limitations" required by the claims, two species is not sufficient to adequately describe the genus of claims which includes any and all such ribonuclease inhibitor variants. The specification also fails to describe additional representative species of these ribonuclease inhibitor variants by sufficient **structural characteristics** or properties other than the activities recited in claim 1 and the disclosed cysteine modifications, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 1-7, 9, 10 and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a mutant ribonuclease inhibitor comprising the amino acid sequence of SEQ ID NO: 3, wherein said mutation is a substitution in one of its two adjacent cysteine residues to an amino acid residue not capable of forming a disulfide bond, the mutant ribonuclease inhibitor having a greater resistance to oxidation, the mutant ribonuclease inhibitor retaining its specificity and binding affinity to ribonuclease, does not reasonably provide enablement for any variant ribonuclease inhibitor having at least one amino acid substitution in at least one of its

adjacent cysteine residues to an amino acid residue not capable of forming a disulfide bond, the mutant ribonuclease inhibitor having a greater resistance to oxidation, the mutant ribonuclease inhibitor retaining its specificity and binding affinity to ribonuclease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

This rejection was stated in the previous office action as it applied to previous claims 1-7, 9, 10 and 15. In response to the previous rejection, applicants have canceled claim 8 and amended claims 1, 9 and 15 and traverse the rejection in combination with the rejection based on a lack of enablement below, as it applies to the newly amended claims.

This rejection under enablement was argued by applicants together with the above rejection under written description and is found non-persuasive for all the reasons stated above with applicants presented arguments.

As stated above, applicant's arguments continue to be along the same principal of reason previously presented. Applicants referred to changes to the claim continue to be directed to the "means by which" the final product is obtained, rather then to the actual final claimed product (i.e. the ribonuclease inhibitor variant or mutant). As these means or processes do not place limitations on the final claimed product, applicants have not thus limited the scope of the claimed product and the scope of the claimed product continues to not be enabled for the reasons previously stated.

With respect to the enablement of the claimed genus, applicants specification does not support the broad scope of the claims which encompass all modifications and fragments of any mutant ribonuclease which **does not** comprise said cysteine mutations because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting ribonuclease inhibitor activity and oxidative resistance; (B) the general tolerance of ribonuclease to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of amino acid modifications of any ribonuclease inhibitor. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of those mutants having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7, 9, 10 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Blazquez et al. (Journal of Biological Chemistry, Vol 271, pp 18638-18642, 1996).

This rejection was stated in the previous office action as it applied to claims previous claims 1-7, 9, 10 and 15. In response to the previous rejection, applicants have amended claims 1, 9 and 15 and traverse the rejection as it applies to the newly amended claims.

For applicant's convenience, the original rejection is repeated here. Blazquez et al. teach a ribonuclease inhibitor which meets all of the structural limitations of the rejected claims and thus anticipates the claims. The ribonuclease inhibitor taught by Blazquez et al. is a "mutant human ribonuclease" having at least one amino acid substitution in at least one of two adjacent cysteine residues present in the amino acid sequence of the wild-type human ribonuclease inhibitor, the substitution being to an amino acid not capable of forming a disulfide bond with an adjacent residue. A greater resistance to oxidation (then the human ribonuclease inhibitor) and the specificity and binding affinity to ribonuclease are inherent properties of the ribonuclease inhibitor taught by Blazquez et al.

While the reference does not specifically disclose that the ribonuclease inhibitor has a greater resistance to oxidation (then the human ribonuclease inhibitor). Since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Applicants have amended the previous claims such that they now require that "the variant differing in amino acid sequence from the native form of the ribonuclease inhibitor only by having at least one amino acid substitution in at least one of two adjacent cysteine residues present in the amino acid sequence of the wild-type inhibitor...". Applicants further traverse the rejection of these claims on the basis that nowhere does the reference Blasquez teach making modified forms of RI for any reason. Applicants continue to acknowledge many of the teachings of Blasquez, however, questions the Examiner's ability to find any passage in the Blasquez paper that discloses making changes to the amino acid sequence of the native protein.

Applicants complete argument is acknowledged and has been carefully considered, however, continues to be found nonpersuasive on the basis that as previously stated "the ribonuclease inhibitor" taught by Blazquez et al. meets all of the structural limitations of the claimed ribonuclease inhibitor.

Blazquez et al. teach the porcine ribonuclease inhibitor, which meets all of the structural limitations of the claimed ribonuclease inhibitor variant or mutant. The porcine ribonuclease inhibitor inherently meets all of the amino acid structural requirements of the claimed ribonuclease inhibitor. If layed side by side, the porcine ribonuclease inhibitor would be structurally identical to that "ribonuclease inhibitor" claimed by applicants and thus it would inherently also maintain all of the functional characteristics associated with such a structurally identical ribonuclease inhibitor.

These structural limits include applicant's most recent amendment requiring that "the variant differing in amino acid sequence from the native form of the ribonuclease inhibitor only by having at least one amino acid substitution in at least one of two adjacent cysteine residues present in the amino acid sequence of the wild-type inhibitor...". It is noted that this amendment is interpreted as the claimed "variant" differs by having or comprising at least one amino acid substitution in at least one of two adjacent cysteine residues present in the amino acid sequence of the wild-type inhibitor...". The reference to "only by having at least one amino acid substitution ...' is somewhat confusing and interpreted as "having or comprising at least one amino acid substitution..." (See above rejection under 112 second paragraph).

Similarly to amended claim 1 applicant's amendments of claims 9 and 15 continue to read on the ribonuclease inhibitor variant taught by Blazquez et al. This is by virtue of applicant's limitations that the claimed variant have "at least one amino acid substitution..." (claim 9) and "... an amino acid substitution in at least two amino acids positions..." (claim 15).

While the reference does not specifically disclose the ribonuclease inhibitor produced by an engineered process (as recited by the claims), the production of a protein by a particular process does not impart novelty or unobviousness to a protein when the same protein is taught by the prior art. This is particularly true when the properties of the protein are not changed by the process in an unexpected manner. See In re Thorpe, 227 USPQ 964 (CAFC 1985); In re Marosi, 218 USPQ 289, 292-293 (CAFC 1983); In re Brown, 173 USPQ 685 (CCPA 1972). Since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Thus claims 1-7, 9, 10 and 15 remain anticipated by Blazquez et al.

Claim 16 is rejected under 35 U.S.C. 102(b) as being anticipated by Lee et al. (Biochemistry, 27, pp 8545-8553, 1988).

Lee et al. teach the isolation and primary structure of human ribonuclease inhibitor comprising the amino acid sequence of SEQ ID NO: 3. It is noted that SEQ ID NO: 3 is the wild-type human ribonuclease inhibitor with no amino acid changes.

Thus, claim 16 is anticipated by Lee et al.

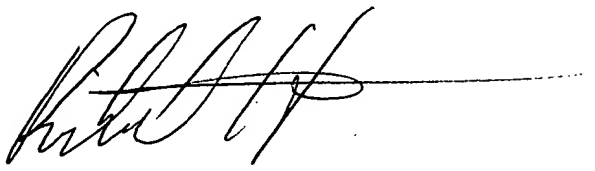
Remarks

No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G. Hutson whose telephone number is (571) 272-0930. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Richard G Hutson, Ph.D.
Primary Examiner
Art Unit 1652

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